UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/031,154	04/24/2002	George N. Cox III	4152-3-PUS	6320

22442 7590 09/25/2008

SHERIDAN ROSS PC
1560 BROADWAY
SUITE 1200
DENVER, CO 80202

EXAMINER
XIE, XIAOZHEN

ART UNIT	PAPER NUMBER
1646	

MAIL DATE	DELIVERY MODE
09/25/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/031,154	COX ET AL.	
	Examiner	Art Unit	
	XIAOZHEN XIE	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 May 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *68,77,78,80-87,89-94,96,102,104,105,125-135 and 137-139* is/are pending in the application.

4a) Of the above claim(s) *87 and 89* is/are withdrawn from consideration.

5)☒ Claim(s) *138* is/are allowed.

6)☒ Claim(s) *68,77,78,80-86,90-94,96,102,104,105,125-135,137 and 139* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *14 January 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

Applicant's amendment of the claims filed 14 May 2007 has been entered.

Claims 1-67, 69-76, 79, 88, 95, 97-101, 103, 106-124 and 136 have been cancelled. Claim 139 has been added. Claims 68, 77, 78, 80-87, 89-94, 96, 102, 104, 105, 125-135 and 137-139 are pending. Claims 87 and 89 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention. Claims 68, 77, 78, 80-86, 90-94, 96, 102, 104, 105, 125-135 and 137-139 are under examination.

Claim Rejections Withdrawn

The rejection of claims 67-68, 77, 80-84, 126-129, 137 under 35 U.S.C. 102(e) as being anticipated by Lauffer et al. (US 2001/0053539), is withdrawn in response to Applicant's amendment of the claims to recite natural erythropoietin and immunoglobulin domain sequences at the junction.

The rejection of claims 90-94, 96, 104, 130-136 under 35 U.S.C. 103(a) as being unpatentable over Lauffer et al. (US 2001/0053539), in view of Mapelli et al. (US 5,519,115), is withdrawn in response to Applicant's amendment of the claims to recite that the fusion protein comprises a natural human erythropoietin (the recitation of "a natural human erythropoietin" is interpreted as the full-length human EPO protein), and Lauffer et al., however, used a truncated human EPO protein.

The rejection of claims 133-135 under 35 U.S.C. 103(a) as being unpatentable over Lauffer et al. (US 2001/0053539), in view of Mapelli et al. (U.S. Patent 5,519,115), and further in view of Qiu et al. (J. Biol Chem., 1998, May 1,273(18):11173-11176), is withdrawn in response to Applicant's amendment of the claims as stated above.

The rejection of claims 78, 86, 102 and 105 under 35 U.S.C. 103(a) as being unpatentable over Lauffer et al. (US 2001/0053539), in view of Sytkowski (U.S. Patent 5,580,853), is withdrawn in response to Applicant's amendment of the claims as stated above.

Claim Rejections Maintained

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The amended claims 126 and 137 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 126 and 137 have been amended to recites "a natural erythropoietin amino acid sequence and a natural immunoglobulin domain amino acid sequence". As set forth in the previous office action, without a SEQ ID or specifying the species where the sequence is generated, e.g., a human, a mouse, a frog or a fish sequence, the metes and bounds cannot be determined. Further, the specification fails to define such sequences.

Applicant argues that claim 125 has been amended to recite that the sequences are from human. However, the newly amended claims 126 and 137 do not have the limitation of "human".

New Grounds of Rejections

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 68, 77, 78, 80-86, 125-129 and137 are rejected under 35 U.S.C. 102(e) as being anticipated by Strom et al. (US 6,165,476, which has a filing date on 10 July 1997).

Strom et al. teach an erythropoietin (EPO) fusion protein wherein an EPO protein is attached to an amino acid sequence comprising an immunoglobulin hinge region sequence (i.e., direct fusion between EPO and an Ig domain), and the fusion protein exhibits increased biological activity (col. 3, lines 12-40). Strom et al. teach that the amino acid sequence of the EPO protein can be wildtype human erythropoietin (col. 13, lines 55-57), and the amino acid sequences of the hinge regions include human immunoglobulin sequences (col. 4, Table). Strom et al. teach pharmaceutical compositions comprising the fusion protein (col. 12, lines 46-60). Strom et al. teach

making the fusion protein using recombinant technology (col. 9, line 31 through col. 12, line 6), and purifying the fusion protein using chromatography (col. 12, lines 7-13). Strom et al. teach that the fusion protein can be in a dimeric form (col. 4, lines 14-19).

Since the specification defines that "the Ig domains include the constant region such as, for example, an IgG-Fc, IgG-C_H, an Fc or C_H domain from another Ig class, i.e., IgM, IgA, IgE, IgD or a light chain constant domain; truncations and amino acid variants or substitutions of these domain also are included" (pp. 7, lines 35-38), and the claim language does not require the Ig domain to be the full-length of the constant region, the Ig domain taught by Strom et al. (i.e., an amino acid sequence comprising the hinge region sequence of the constant region) meets the limitation recited in the instant claims. Also, because the claim language uses the open-ended transitional term "comprising", it does not exclude additional component in the fusion protein, e.g., EPO-Ig hinge region-EPO.

While Strom et al. do not expressly teach an EC_{50} value as recited in the claims for the fusion protein, this activity is inherent to the protein since it has the same structure as claimed. A compound and all of its properties are inseparable (*In re Papesch*, 315 F.2d 381, 137 USPQ 43 (CCPA 1963)).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

> invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 90-94, 96, 102, 104, 105, 130-132 and 139 are rejected under 35 U.S.C. 103(a) as being unpatentable over by Blumberg et al. (US 6,485,726 B1, which was filed on 24 July 1998, and has a priority date on 17 January 1995), in view of Mapelli et al. (U.S. Patent 5,519,115, issued on 21 May 1996).

Blumberg et al. teach conjugating an erythropoietin (EPO) to an Fc fragment of the constant region of an immunoglobulin, such that the fusion protein can bind to the FcRn receptor and be transported across the epithelial barrier by FcRn mediated-transport (col. 3, lines 41-52; col. 12, line 42 bridging col. 13, line 1). Blumberg et al. teach an example of EPO-Fc fusion, in which the entire mouse EPO sequence was linked at its C-terminus to the Fc fragment through an Ala-Ala-Ala linker (col. 13, lines 1-31). Blumberg et al. teach that the DNA encoding EPO may be replaced with DNA encoding any of the other proteins, including human EPO taught in US 4,703,008, by using standard technique to create an Fc fusion protein (col. 13, lines 32-36; col. 12, lines 53-54). Blumberg et al. teach recombinant expression and purification of the fusion protein (col. 8, lines 5-20; col. 17, lines 52-54). The EPO-Fc fusion is in a dimeric form because this property is immaterial to the Fc fragment, which forms a disulfide bond to bring two monomers together (see Strom et al., US 6,165,476, col. 4, lines 14-19).

Blumberg et al., however, do not teach a peptide linker that consists of a mixture of 2, 4, or 7 amino acid residues, selected from the group consisting of glycine and serine (claims 92, 131,132); wherein the peptide linker is SerGly, or SEQ ID NO: 1 (claims 93, 94).

Mapelli et al. teach the use of a small bridge, e.g., small bridges of 5 amino acids or less, in the construction of oligopeptides (col. 24, lines 21-24). Mapelli et al. teach that these small bridges prevent disadvantageous steric hindrance between discrete monomers, and provide a sufficient degree of flexibility to the oligopeptide to allow for the formation of advantageous conformations (col. 24, lines 7-20). Mapelli et al. teach that Gly side chain moieties are unlikely to sterically hinder any potential folding of the oligomer, and cannot participate in energenically stable bond structure (col. 24, lines 53-63). Mapelli et al. further give several example of such Gly-rich linkers, e.g., bridges having 2 and 4 amino acids, Ser-Gly-Gly-Ser (identical to SEQ ID NO: 1) (col. 25, line 6), and Ser-Gly (col. 27, line 23).

It would have been obvious to one of the ordinary skill in the art at the time the invention was made to combine the teachings of Blumberg et al., with those of Mapelli et al., to use small Gly-rich linkers, such as Ser-Gly-Gly-Ser (SEQ ID NO: 1) or Ser-Gly, for conjugating an EPO with the Fc fragment. One of ordinary skill in the art would have been motivated to combine the teachings, because Blumberg et al. teach that an EPO-Fc conjugation can improve pharmacokinetic properties, and Mapelli et al. teach that small Gly-rich bridges of 5 amino acids or less, such as SerGly or Ser-Gly-Gly-Ser (SEQ ID NO: 1), are particularly useful in the construction of oligopeptides because they prevent disadvantageous steric hindrance and provide a sufficient degree of flexibility to the oligopeptide to allow for the formation of advantageous conformations. Therefore, the combined teachings provide a reasonable expectation of successfully linking the two

polypeptide components without affecting the structure and biological activity of the resulting fusion protein.

Further, the recitation of specific EC_{50} of the fusion protein (e.g., claims 90, 96 and 139 recite that EC_{50} is within 4 fold of that of non-fused EPO; EC_{50} is less than about 1000 ng/ml; or EC_{50} is indistinguishable from that of the natural human EPO) does not render the invention patentable. Applicant has provided quantitative data, however, it has been established that the invention is obvious. As such, Applicant has worked out experimental details that are immaterial to the claimed invention. "Mere recognition of latent properties in the prior art does not render nonobvious an otherwise known invention" (see MPEP 2145 [R-2] and *in re* Wiseman, 596 F.2d 1019, 201 USPQ 658).

Applicant argues that Mapelli et al. teach the use of peptide linkers for the construction of a bridge to form oligopeptides, in which relatively small monomer peptides ranging from 4 to 37 amino acids and having antimicrobial activity are linked together. Applicant argues that Mapelli et al. teach that the bridge must be capable of promoting intermonomer interactions amongst the monomer in a specific oligopeptide. Applicant argues that the Mapelli et al. reference is not directed to the production of fusion proteins, such as EPO-Ig fusion protein, which is a fusion of two large proteins with very different structure. Applicant argues that the EPO-Ig fusion proteins are far more complex than the simple oligomers contemplated by Mapelli et al., because EPO-Ig fusion proteins also interact to form disulfide-linked dimers, which can negatively affect their bioactivity. Applicant argues that Mapelli et al. do not teach or suggest the

use of full length proteins, and that the requirement for the oligopeptides to be transported across cell membrane is not a concern for the EPO-Ig fusion proteins.

Applicant's arguments have been fully considered but have not been found to be persuasive.

As set forth previously and above, Mapelli et al. teach that small bridges, e.g., 5 amino acids or less, prevent disadvantageous steric hindrance between discrete monomers, and provide a sufficient degree of flexibility to the oligopeptide to allow for the formation of advantageous conformations, and Mapelli et al. also teach that Gly side chain moieties are unlikely to sterically hinder any potential folding of the oligomer, and cannot participate in energenically stable bond structure. Mapelli et al. teach that these Gly-rich linkers can be used to link two peptide monomers and form an oligomer with a functional conformation. Although Mapelli et al. do not expressly teach using these Gly-rich linkers to link EPO and an Ig domain, it would have been obvious to one of the ordinary skill in the art to do so, because preventing steric hindrance between discrete monomers, and providing a sufficient degree of flexibility to allow for the formation of advantageous conformations is required for any fusion protein, no matter it is a oligopeptide or oligopolypeptide. Mapelli et al. teach that small Gly-rich linkers mmet these requirement. Further, a correct conformation provides the functions and activities of the molecules, no matter how complex they are.

Claims 133-135 are rejected under 35 U.S.C. 103(a) as being unpatentable over Blumberg et al. (US 6,485,726 B1), in view of Mapelli et al. (U.S. Patent 5,519,115), and further in view of Qiu et al. (J. Biol. Chem., 1998, May 1,273(18):11173-11176).

Blumberg et al. and Mapelli et al. teach as set forth above. They, however, fail to teach using a peptide linker that consists of 7 amino acid residues selected from the group consisting of glycine and serine for the conjugation (claims 133-135).

Qiu et al. teach the use of a sequence encoding 3 to 7 glycine residues for the construction of a dimeric EPO (pp. 11174, Fig 1). Qiu et al. teach that the polyglycine linker can confer a functional conformation for the EPO dimer molecule (pp. 11176, Fig. 6).

It would have been obvious to one of the ordinary skill in the art at the time the invention was made to combine the teachings of Blumberg et al., with those of Qiu et al., to use a polyglycine linker with 3-7 glycine residues to link an EPO and an Ig-Fc domain. One of ordinary skill in the art would have been motivated to combine the teachings, because Blumberg et al. teach that an EPO-Fc conjugation can improve pharmacokinetic properties, and Qiu et al. showed that polyglycine linkers consisting of 3-7 glycine residues that can confer a functional conformation for an EPO-conjugate containing two monomers. Therefore, the combined teachings provide a reasonable expectation of successfully linking the two polypeptide components without affecting the structure and biological activity of the resulting fusion protein.

Applicant argues that Qiu et al. reported that EPO-EPO fusion proteins joined by peptide linkers of 3-7 glycine residues have significantly reduced biological activities (4-

10 folds) relative to wild type EPO. Applicant argues that Qiu et al. do not teach that linking the components will not affect the structure and biological activity of the fusion. Applicant further argues that the literature teaches that the size and sequence of peptide linkers can dramatically affect bioactivities of fusion protein, for examples, Robinson et al. (Proc., Natl. Acad. Sci., USA 1998, 95:5929-5934) teach that only linkers with 13 or more amino acids resulted in biologically active fusion protein, and Chang (US 5,723125) teaches that the length of the linker can dramatically impact the biological activity of an IFN-α/IgG-Fc fusion protein, and that longer peptides linkers are preferred.

Applicant's arguments have been fully considered but have not been found to be persuasive.

Qiu et al. reported that a dimeric wildtype EPO molecule linked by 7 glycine residues had a similar biological effect as the wildtype monomeric EPO, and that dimeric mutant EPO molecules, however, had a dramatic increase in biological acitvity than the mutant monomer (pp. 11174, col. 1, last paragraph bridging col. 2). Qiu et al. reported that for monomeric WT EPO, EC_{50} = 105 milliunits/ml, and for dimeric WT EPO, EC_{50} = 185 milliunits/ml, which is within 4 fold of EC_{50} non-fused EPO. Therefore, it would have been obvious to one of the ordinary skill in the art to use such linker, because Qiu et al. showed that the polyglycine linkers can provide a functional conformation for an EPO-conjugate containing two monomers.

With regard to the literature that Applicant cited, Blumberg et al., however, already teach a successful conjugation between a full-length EPO and the Fc fragment by using a three amino acids linker, Ala-Ala-Ala.

Conclusion

CLAIM 138 IS ALLOWABLE.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Xiaozhen Xie whose telephone number is 571-272-5569. The examiner can normally be reached on M-F, 8:30-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary B. Nicole, Ph.D. can be reached on 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Xiaozhen Xie, Ph.D.
September 14, 2008

/Elizabeth C. Kemmerer/
Primary Examiner, Art Unit 1646